PATENT COOPERATION TREA 10/538277

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION See Form PCT/IPEA/416	
International application No. PCT/MX 03/00108	International filing date *(day/month/year)* 11.12.2003	Priority date *(day/month/year)* 13.12.2002
International Patent Classification (IPC) or national classification and IPC A61K35/78		
Applicant UNIVERSIDAD AUTONOMA METROPOLITANA et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 2 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
08.07.2004	17.06.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Escolar Blasco, P Telephone No. +49 89 2399-7331

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/MX 03/00108

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-9	as originally filed

Claims, Numbers

1-9	received on 08.07.2004 with letter of 05.07.2004
10-18	received on 06.06.2005 with letter of 31.05.2005

Drawings, Sheets

1/1	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/MX 03/00108

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-18
	No:	Claims	
Inventive step (IS)	Yes:	Claims	7-9,17-18
	No:	Claims	1-6,10-16
Industrial applicability (IA)	Yes:	Claims	1-18
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Comments on item V

1. Reference is made to the following documents:

   D1: SOTO C. P. ET AL: "Prevention of alloxan-induced diabetes mellitus in the rat by silymarin." COMPARATIVE BIOCHEMISTRY AND PHYSIOLOGY, PART C: PHARMACOLOGY & ENDOCRINOLOGY, vol. 119c, no. 2, 1998, pages 125-129

   D2: SCHOENFELD VON J ET AL: "Silibinin, A Plant Extract with Antioxidant and Membrane Stabilizing Properties, Protects Exocrine Pancreas From Cyclosporina Toxicity" CMLS, CELLULAR AND MOLECULAR LIFE SCIENCES, BIRKHAUSER VERLAG, BASEL, CH, vol. 53, no. 11/12, December 1997, pages 917-920

2. The subject-matter of claims 1-18 is novel and industrially applicable.

3. Claims 1-6 refer to a composition containing Silymarin and Carbopol plus a pharmaceutically acceptable vehicle. Compositions with silymarin and a vehicle for oral administration are known in the art (see first two lines of p. 126 in D1). Hence, the claimed composition differs from the known ones only in the presence of Carbopol. Since this difference does not provide any particular technical effect (according to the applicant, carbopol provides stable silymarin suspensions, but the fact is that carboxymethyl cellulose is known as a suspension stabilizer), the problem to be solved is the obtention of an alternative orally administrable silymarin composition.
   Once an active ingredient is known, the addition of appropriate excipients is part of the routine of the skilled person and implies an inventive effort only in particular cases where a difficulty or a prejudice is overcome. This does not seem to be the case here, since it is not apparent whether carbopol provides any unexpected advantage vis-à-vis carboxymethyl cellulose (vehicle used in D1).
   Hence, the subject-matter of claims 1-6 lacks an inventive step.

4. The process of claims 10-16 for obtaining the silymarin composition of claims 1-3 appears to comprise steps which are common in the field of galenics. Again, there

seems to be no unexpected technical effect cited in the description in relation with the choice of this particular process and percentage ranges. No inventive step can be acknowledged for claims 10-16.

5. Claims 7 to 9 and 17-18 relate to further medical uses of the composition of claim 1. They seem to involve an inventive step for the following reasons:

D1 discloses that silymarin has a favourable effect on the pancreatin damage produced by the production of free radicals in an experimental model of diabetes mellitus, and probably in diabetes mellitus type I (see p.129). D2 discloses in the abstract that this drug protects the exocrine pancreas from cyclosporin toxicity. The difference between the claimed subject-matter and the prior art resides thus on the probed regenerative effect of damaged pancreatic cells. The technical effect of this difference is that silymarin is useful for treating diabetes (and not only for preventing it) and particularly useful in cases wherein a regeneration of damaged pancreatic cells is needed. The prior art reported that silibilin "could be useful in the treatment of non-insulin-dependent diabetes mellitus" but provided no solution to the problem of providing a regenerative treatment for pancreatic cells.

CLAIMS

Having described the invention, it is considered an innovation and therefore the contents of the following clauses are claimed as property:

1. Pharmaceutical composition characterized by containing Silymarin and Carbopol and a pharmaceutically acceptable vehicle.

2. Composition in accordance with claim 1 characterized by containing 3 to 7% Silymarin and 0.2 to 0.6% Carbopol.

3. Composition in accordance with claim 2 where it preferably contains 5% Silymarin and 0.5% Carbopol.

4. Composition in accordance with claims 1 to 3 where the pharmaceutical composition may be in the form of an oral dose.

5. Composition in accordance with claim 4 where the oral form may be a suspension, oral solution, emulsion, gel, hard gelatin capsule, soft gelatin capsule, immediate release tablet, controlled release tablet, prolonged release or sustained release tablet.

6. Composition in accordance with claim 5 where it is preferably in the form of an oral suspension.

7. The use of the composition of claim 1 based on Silymarin and Carbopol for the manufacture of a medicine that is useful in the regeneration of damaged pancreatic cells, for the recovery of the endocrine pancreatic function.

8. The use in accordance with claim 7 where the functioning of the ß-pancreatic cells causes the production of insulin.

9. The use in accordance of claim 8, where the medicine is useful for the treatment of diabetes mellitus.

10. Procedure for obtaining the composition of claims 1 to 3 consisting of the following steps:

a)Dissolution of 0.2 to 0.6% of Carbopol in deionized water, subjecting it to agitation for a period of time of 50 to 90 minutes.

b)Addition of Silymarin in a percentage of 3 to 7 to the foregoing dissolution and subjected to agitation for a minimum period of one hour until a homogenous mixture is obtained.

11. Procedure in accordance with claim 10 where preferably 0.5% of Carbopol and 5% of Silymarin are dissolved.

12. Process in accordance with claim 10 where it optionally has a subsequent step of solubilization.

13. Process in accordance with claim 10 where it optionally has a subsequent step of emulsification.

14. Process in accordance with claim 10 where it optionally has a subsequent step of gelation.

15. Process in accordance with claim 10 where it optionally has a subsequent step of encapsulation.

16. Process in accordance with claim 10 where it optionally has a subsequent tablet-making step.

17. The use in accordance with claims 7, 8 and 9 where the administration dose is from 60 to 220 mg/Kg.

18. The use in accordance with claim 17 was the preferred dose is 200 mg/Kg.